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Neuroimaging of VTA-seed-connectivity to predict outcome in adult ADHD

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ADHD is a developmental psychiatric disorder of childhood that can persist into adulthood. Since dopaminergic stimulants have a high effectiveness in treatment, the importance of the dopaminergic reward system in pathogenesis has long been discussed [1]. As part of the EU project CoCA, we addressed the alteration of the connectivity of the reward system in adult ADHD in two projects. In previous work, we established the validity of a seed-connectivity workflow from the ventral tegmental area (VTA) [2]. Most neuroimaging studies in ADHD simply document differences between healthy controls and cases. However, we wondered whether a fMRI-measurement is able to predict longitudinal outcome in a short to medium time span (three month) as well as longer time span of two years.

First, we investigated in n=30 participants of a clinical trial with fitness and light therapy whether connectivity between dopaminergic core areas (VTA) of the brainstem and the rest of the brain predicts therapeutic outcome. Participants participated in the PROUD trial, a non-pharmacological investigation of aerobic fitness therapy and bright light therapy [3]. Second, we examined n=54 patients of our ADHD consultation 2-3 years after an fMRI measurement by means of a clinical interview with regard to general psychopathology as well as ADHD-specific symptoms. Our hypothesis was, that baseline VTA-connectivity predicts outcome independent of medication.

Patients received clinical interviews (DIVA, IDS-C30, CGI) as well as a variety of self-rating scales. Medication and comorbid disorders were recorded. We used a 3 Tesla Siemens PRISMA scanner to conduct an 8 min resting-state functional magnetic resonance investigation. We conducted paired-t-test for pre-post testing and regression analysis for correlation with individual clinical scores. Multiple testing was accounted for by using a cluster-forming threshold of $p < 0.001$ and $pFDR < 0.05$ for cluster. Analysis was done in SPM12 and the CONN toolbox V20b. Most patients in the second group (n=54) received stimulant medication (n=33).

In the PROUD study, VTA-connectivity to the occipital lobe demonstrated was significantly higher at baseline in patients who became better in terms of ADHD symptoms over the course of 3 month. Connectivity to the superior frontal gyrus was lower in those with less symptoms after 3 month.

In the longer study (n=54), patients receiving stimulant medication had higher VTA-occipital lobe connectivity when their psychosocial functioning (GAF) was better after 2 years follow-up. This was reversed in patients without treatment. As this study was not randomized, we speculate that patients receiving medication were more ill and more in need of treatment.

In summary, two longitudinal follow-up studies demonstrate the potential of the VTA-connectivity to predict outcome of a clinical interventions (PROUD-trial) as well as a long-term follow-up over almost 2 years. Future analysis should look into the connectivity change not over this time span and complement the univariate analysis with a machine learning model and a receiver-operating curve. The connectivity between occipital lobe and VTA might be a proxy of attribution of salience to visual stimuli and consecutive attentional processes.

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Association between diet and impulsivity in ADHD – results of the Eat2beNice-APPetite study

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Introduction: The influence of our diet on mental health is of increasing importance in current research. Study results on the gut-brain axis suggest that the gut microbiome can influence mental processes via neuronal, hormonal and immune signaling pathways [1]. The gut microbiome is largely influenced by our diet. Some studies provide evidence that a "Western diet" rich in saturated fat and sugar may promote mental disorders [2]. There is evidence, that dietary behaviour in individuals with Attention Deficit Hyperactivity Disorder (ADHD) is characterized by an increased intake of sugar and saturated fat [3]. So far, it is unclear whether this dietary pattern contributes to ADHD symptoms such as impulsivity. The aim of this study is to investigate the influence of certain macronutrients such as fats and mono/disaccharides on impulsivity in individuals with ADHD. Using our APPetite-mobile-app [4] enabled us to study dietary behaviour and momentary impulsiveness in everyday life of our participants.

Methods: 43 participants with ADHD (mean age 36.0 ± 12.3 years, 21 females) and 186 healthy controls (mean age 28.5 ± 7.7 years, 133 females) without any psychiatric condition were included into the study. Food intake was recorded over a period of three days using the APPetite-mobile-app via a 6 step process: (1) Selection of meal type, (2) Entry of time of meal, (3) Selection of consumed foods and drinks, (4) Specification of consumed amounts, (5) Presentation of reminder for commonly forgotten foods, and (6) Indication of predominant reason for eating. In addition to entering consumed foods in the APPetite-mobile-app, subjects completed an online food log for the last 24 hours (myfood 24) at the beginning of the study. After the data collection period, a detailed analysis of the ingested nutrients was performed for each subject. Trait impulsivity was assessed using the UPPS-P, a self-assessment questionnaire. Momentary impulsiveness was assessed via the mHealth APP by means of the Momentary Impulsiveness scale (MIS). The MIS consists of 4 questions capturing different aspects of impulsivity. The participants were prompted to answer these questions at 8 semi-random times per day between 8 AM and 10 PM. The minimum time between 2 prompts was 1 hour. Thereby participants could not predict the exact time of the next prompt and the assessed situations are a better reflection of the participant's real life.

Results: ANOVA revealed higher levels of both, trait and momentary impulsivity in individuals with ADHD compared to controls ($p < 0,01$). After preprocessing of data that was sampled via the mHealth APP is completed, a regression analysis with different macronutrients as predictors and impulsivity as dependent variable will be computed. To assess the association between momentary impulsiveness and dietary intake, generalized linear multilevel modelling will be used. Results of these analyses will be presented.

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The effect of emotional problems on the attention and frontal lobe functions in children with attention deficit hyperactivity disorder

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Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which is associated with frontal lobe dysfunction. Also, many ADHD children have co-morbid emotional problems such as depression, anxiety, and irritability. Previous research showed that family members of ADHD children tended to have higher prevalence of major depressive disorder than those without ADHD. Since some symptoms of ADHD children such as inattention, and irritability are likely to be symptoms of depression in addition to ADHD, it is difficult to accurately diagnose and treat those co-morbid conditions.

Aims: This study investigated the effect of emotional problems on attention and frontal lobe functions including response inhibition, processing speed, cognitive flexibility and divided attention in children with ADHD.

Methods: The participants were 59 children who visited the department of child and adolescent psychiatry at a university hospital in Seoul, and were diagnosed with ADHD based on the diagnostic statistical manual of mental disorder-5(DSM-5) criteria by child psychiatrists. Their age range was 8–15 years. Most of ADHD children included in this study were ADHD, combined presentation. We included children with a full-scale intelligent quotient (FSIQ) of 70 or higher and a language comprehension score of 80 or higher on the Korean version of wechsler intelligence scale for children-IV(WISC-IV). They were individually administered the Korean versions of attention and frontal lobe function tests including continuous performance test(CPT), children's color trails test -1, 2(CCTT-1, 2), & stroop color and word test by licensed clinical psychologists. Their mothers completed the Korean versions of the DSM-5 level 2 cross-cutting symptom measures – depression, anxiety, anger, and irritability-affective reactivity index (ARI). This study was conducted after the permission was obtained from the institutional review board(IRB) of Seoul national university hospital. Regression analysis were performed on the data using SPSS 20.0 software.

Results: It was found that DSM-5 level 2 cross-cutting symptom anxiety scores were negatively associated with the CCTT-1 scores assessing speed of visual scanning and attention ($P < .048$), while the depression scores were associated with the omission error T-scores of visual CPT (inattention) and the response time T-scores of auditory CPT (processing speed) in ADHD children, respectively ($P < .008$, $P < .015$). The effects of the DSM-5 level 2 cross-cutting symptom anger, and irritability scores were not significant on the performances of CPT, CCTT-1, 2, & stroop color and word test assessing frontal lobe functions. These results suggest that poor executive functions like response disinhibition and cognitive inflexibility that ADHD children show might be primarily caused by frontal lobe dysfunction, not by emotional instability like anger and irritability.

Conclusion: Depression and anxiety rather than anger and irritability might be more associated with inattention and slow processing speed on neuropsychological tests in ADHD children. Further study is needed to compare the performances on neuropsychological tests between ADHD children with co-morbid depression and anxiety and pure ADHD children.

Conflict of interest

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Microdosing with psychedelics to self-medicate for ADHD symptoms in adults: a prospective naturalistic study

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Attention Deficit Hyperactivity Disorder (ADHD) in adulthood is often overlooked, which negatively affects the individual's well-being. First-line pharmacological interventions are effective in many ADHD patients, relieving symptoms rapidly. However, there seems to be a proportion of individuals who discontinue, or fail to respond to these treatments. For these individuals, alternative treatment options should be explored. The use of classic psychedelics in low, repeated doses, so called microdosing (MD) is gaining popularity. Individuals engaging in this MD practice reported to do this to self-treat mental and/or physiological disorders. A retrospective survey study showed that MD was rated as being more effective than conventional treatments for ADHD. The current online prospective study aimed to measure the effect of MD on ADHD symptoms, well-being and temporal processing, since this cognitive domain is often impaired in ADHD, by using validated measures and a cognitive task. Adults diagnosed with ADHD, or adults who experienced ADHD symptoms that interfered with daily life, who had the intention to start MD on their initiative to self-treat their symptoms were measured before MD and two- and four weeks later. We expected to find a decrease in ADHD symptoms, an increase in well-being, and enhanced performance on a time perception task after MD. We explored if conventional medication use alongside MD and comorbidities alongside ADHD influenced the effect of MD on ADHD symptoms, well-being and time perception. Also, we explored what proportion of the sample did not improve in ADHD symptoms after MD compared to baseline. Sample sizes included $N=226$ at baseline, $N=65$ at the two-week time point, and $N=46$ at the four-week time point. We found decreased ADHD symptoms after two weeks of MD compared to baseline and symptoms were further decreased at the four-week time point. Respondents using conventional medication alongside MD showed less decrease in ADHD symptoms at the two-week time point compared to those not using medication alongside MD. ADHD symptoms did not differ between those respondents at the four-week time point. Having comorbid diagnoses alongside ADHD did not change the effect of MD on ADHD symptoms. After four weeks of MD, 19.6% of the sample did not show any improvements in ADHD symptoms. Well-being was increased after two weeks of MD and remained at this level two weeks later. Using conventional medication or having comorbid diagnoses did not influence the change in well-being after MD. The changes in ADHD symptoms and well-being were negatively correlated at both the two- and four-week time points. No enhancement of performance on the time perception task was found. Time perception was only affected in individuals using conventional medication alongside MD, indicated by over-reproducing the shortest (1000 ms) time interval at the two- and four-week time points. Placebo-controlled experimental studies are needed to explore further whether there is a beneficial effect of MD in individuals with ADHD, beyond the placebo-effect.

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Effect of pharmacological treatment on health-related quality of life in ADHD and its relationship with treatment efficacy and safety

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Introduction: Health-related quality of life (HRQOL) is a multi-dimensional concept involving individual's perceived physical, mental, and emotional health, and social functioning over time. It is unclear whether pharmacological treatment improves HRQOL in patients with Attention Deficit Hyperactivity Disorder (ADHD). Furthermore, it is not known how the efficacy of these interventions on ADHD symptoms and their safety impact on HRQOL.